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TITLE: TREATMENT OF ADULT SEVERE TRAUMATIC BRAIN INJURY USING AUTOLGOUS BONE MARROW MONONUCLEAR CELLS

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14. ABSTRACT
Traumatic brain injury (TBI) contributes to 50% of all trauma deaths. The mortality rate for adults following severe TBI (Glasgow Coma Scale < 9) is estimated to be 33%. There is currently no therapy to reverse the primary injury associated with TBI. Over the past 10 years there has been a growing body of literature supporting the use of various progenitor cell types to treat acute neurological injuries such as TBI. Our primary hypothesis is that bone marrow mononuclear cell (BMMNC) autologous transplantation after TBI is safe (harvest and infusion related toxicity) after TBI. Our secondary hypothesis is that functional outcomes measures will improve after BMMNC infusion, (3) BMMNC infusion will reduce BBB permeability, and (4) BMMNC is neuroprotective and preserves grey matter and white matter volumes after TBI. Patients, ages18 to 55 years old, admitted to Memorial Hermann Hospital Trauma Center with Glasgow Coma Scores (GCS) of 5 to 8 are screened. This is a dose-escalation study consisting of 4 cohorts including a control group (5 subjects/cohort). The first five subjects will not undergo the bone marrow harvest procedure; though they will be followed and treated the same as the other study participants and complete all follow-up procedures. Subjects are followed for safety, have plasma and CSF (if available) collected for neuroinflammatory markers, and at 30-days and 6 months post-injury, neuropsych and functional outcomes testing and DTMRI are performed. To date, 12 subjects have been enrolled (all controls) and have had plasma collected for neuroinflammatory markers and have returned for their 30-day follow-up visits. 6 subjects have completed their 6 month follow-up assessments.

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Traumatic Brain Injury, Bone Marrow Mononuclear Cells

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TREATMENT OF ADULT SEVERE TRAUMATIC BRAIN INJURY USING

AUTOLOGOUS BONE MARROW MONONUCLEAR CELLS

Annual Progress Report (01-June-2012 to 30-June-2013)

Introduction:

Traumatic brain injury (TBI) contributes to 50% of all trauma deaths. The mortality rate for adults following severe TBI (Glasgow Coma Scale < 9) is estimated to be 33%. There is currently no therapy to reverse the primary injury associated with TBI. Over the past 10 years there has been a growing body of literature supporting the use of various progenitor cell types to treat acute neurological injuries such as TBI and stroke. Neural stem cells (adult and embryonic), mesenchymal stromal and multipotent adult progenitor cells, and bone marrow mononuclear cells (from which MSC and MAPCs are derived) have all shown efficacy in pre-clinical models of TBI/stroke through various mechanisms; however, few groups believe that true neural replacement and integration are the putative mechanisms involved in the observed efficacy. More likely is that the progenitor cell populations are modifying the regional response to injury (inflammatory/reparative vs. regenerative), resulting in improved functional outcomes. Our primary hypothesis is that bone marrow mononuclear cell (BMMNC) autologous transplantation after TBI is safe (harvest and infusion related toxicity) after TBI. Our secondary hypotheses are that functional outcomes measures will improve after BMMNC infusion, (3) BMMNC infusion will reduce BBB permeability and (4) BMMNC is neuroprotective and preserves grey matter and white matter volumes after TBI.

Body:

Patients, ages18 to 55 years old, admitted to Memorial Hermann Hospital Trauma Center with Glasgow Coma Scores (GCS) of 5 to 8 are screened. Those patients meeting inclusion/exclusion criteria (or their Legal Authorized Representative [LAR]) are offered consent to participate by the investigator. This is a dose-escalation study consisting of 4 cohorts including a control group (5 subjects/cohort). The first five subjects did not undergo the bone marrow harvest procedure (all 5 enrolled); though they were followed and treated the same as the other study participants and complete all follow-up procedures. Subjects 6-10 received the lowest dose target of $6X10^6$ mononuclear cells/kilogram body weight (all 5 enrolled). Subjects 11-15 have/will receive $9x10^6$ mononuclear cells/kilogram body weight (2 enrolled in this cohort to date), and lastly Subjects 16-20 will receive $12X10^6$ mononuclear cells/kilogram body weight. All subjects will be followed for safety, have plasma and CSF (if available) collected for neuroinflammatory markers, and will return at 30-days and 6 months post-injury for neuropsychiatric and functional outcomes testing and DTMRI.

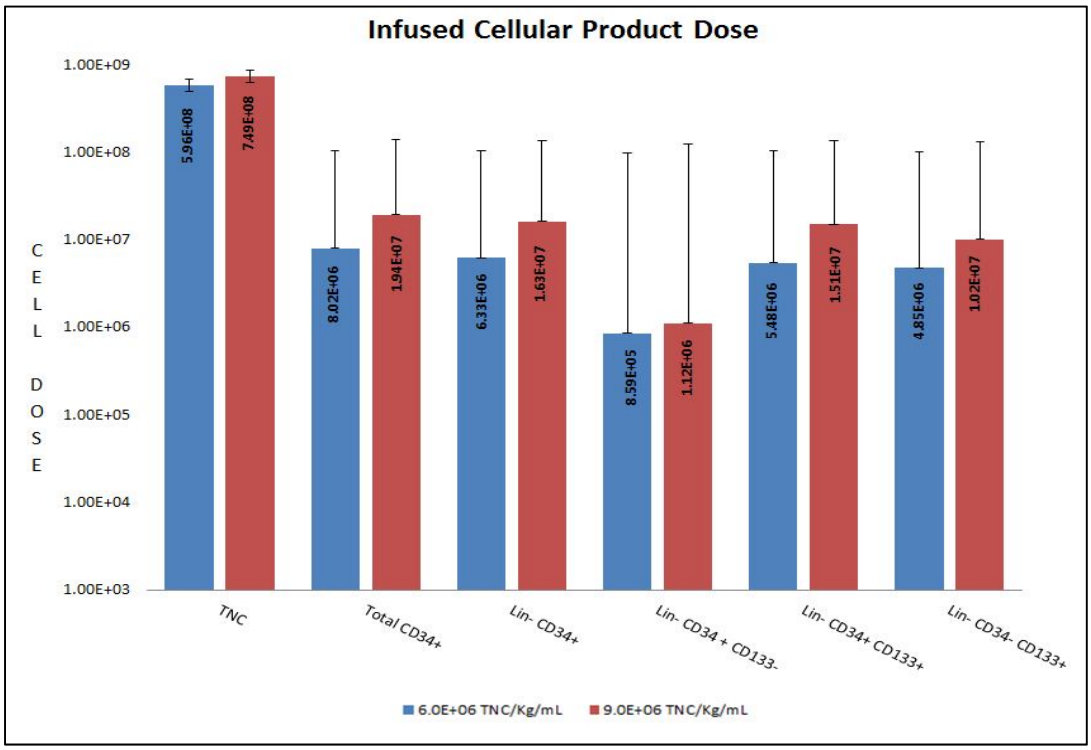
Results to date:

<u>Cellular Product and Dosing Data:</u>

1. Infused Cellular Product Dose

The cellular dose infused at 6 and 9 x 10^6 total nucleated cells (TNC)/Kg of body weight is shown as mean + standard error (SE) on a log-scale of cell numbers. The infused MNC-enriched fraction contains early hematopoietic progenitor cells in the doses shown in Figure 1.

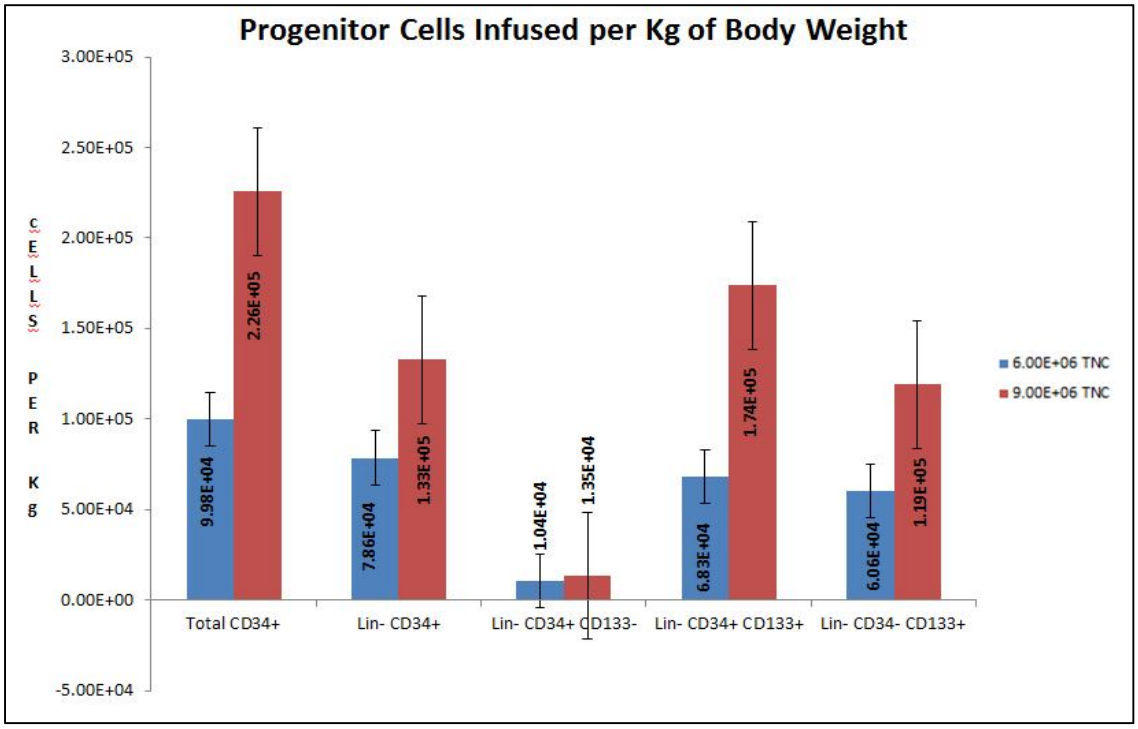
Figure 1



2. Progenitor Cells Infused per Kg of Body Weight

Early hematopoietic progenitor cell doses contained in 6 and 9 x 10^6 TNC (dose per Kg of body weight) of infused cellular product are shown as mean ± SE in Figure 2.

Figure 2



3. Flow Cytometric Analysis of Infused Cellular Product

Cellular viability, immunophenotyping and extended differential leukocyte counts of cellular product infused at 6 and 9 x 10^6 TNC/Kg of body weight are shown below in Figure 3 as mean percentages ± SE

Figure 3

Flow Cytometric Analysis of Infused Cellular Product

Marker	Mean % ± Standard Error (SE) 6 x 10^6 TNC/Kg n = 5	Mean % ± Standard Error (SE) 9 x 10^6 TNC/Kg n = 2
Cell Viability (by 7-AAD staining)	94.41 ± 1.35	96.47 ± 2.23
Total CD34+	1.91 ± 0.35	2.55 ± 0.33
Lin- CD34+	1.51 ± 0.26	2.11 ± 0.39
Lin- CD34+ CD133-	0.20 ± 0.06	0.16 ± 0.02
Lin- CD34+ CD133+	1.31 ± 0.24	1.95 ± 0.42
Lin- CD34- CD133+	1.13 ± 0.26	1.35 ± 0.14
T cells [CD 3+]	65.43 ± 4.59	72.88 ± 0.11
B cells [CD 19+]	19.61 ±4.24	14.14 ±4.44
NK cells [CD56+ CD16+ CD3-]	10.84 ±1.43	7.89 ± 2.73
4 Part Differential		
Lymphocytes	29.97 ±3.20	38.82 ±2.23
Monocytes	33.00 ±2.91	17.91 ±2.59
Granulocytes	23.09 ±3.37	26.79 ±3.30
Blasts	5.32 ±0.61	7.17 ±0.07

<u>Primary Outcome</u>

1. Safety

Figure 4 – Subjects 1-12 Safety Data, Baseline through Day 7

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 1								
GCS	6T	9T	10T	11T	11T	11T	10T	11T
Pao2/FiO2	445	548	325	395	405	100 sat	99 sat	98 sat
AST	148	196	163	135	108	80		95
ALT	47	66	63	60	61	63		157
WBC	12.8	11	7.5	8.5	10.4	10.1	12.8	11.6
HgB	12.2	8.3	8	7.9	7.1	7.7	8.6	7.5
Platelets	254	183	159	176	218	258	367	369
Cr	0.9	0.6	0.7	0.7	0.6	0.6	0.7	0.7
INR	1.26	1.45	1.43	1.34	1.44		1.2	1.2

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 4								
GCS	6T	6T	7t	6t	6t	6t	6t	6T
Pao2/FiO2	492	530	597	100 sat	100 sat	530	411	98 sat
AST	563	90	43	29	86	268		93
ALT	432	194	124	95	116	314		339
WBC	14	10.3	8.3	7.1	9	10.3	10.7	10.1
HgB	13.2	9.4	7.6	7.6	9.8	9.8	9.7	10
Platelets	181	97	83	108	132	147	202	271
Cr	0.7	0.6	0.5	0.5	0.5	0.3	0.5	0.4
INR	1.11	1.32	1.4	1.01	1	0.96	1.01	1

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 2								
GCS	6T	8T	8T	14	15	15	15	15
Pao2/FiO2	598	100 sat	100 sat	100 sat	100 sat	100 sat		100 sat
AST	35	22	22	26	20			16
ALT	35	14	18	22	16			18
WBC	15.3	11	9.5	9.9	8.4	8.5		10.6
HgB	13.5	7.4	7.2	7	7.1	7.8		7.9
Platelets	201	122	89	122	172	254		523
Cr	1.2	1	1.1	0.9	1	0.9		0.9
INR	1.19	1.44	1.42	1.4	1.27			1.11

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 5								
GCS	7T	6T	6T	7T	7T	9T	11T	10T
Pao2/FiO2	304	342	216	100 sat	98 sat	100 sat	98 sat	96 sat
AST	85	33	24	18	20	129		20
ALT	138	80	54	46	44	48		44
WBC	4.4	11.8	10.2	9.9	9.6	16.2	17.3	12.3
HgB	12.8	11.4	11.2	11	11.5	12.3	11	10.3
Platelets	230	169	164	181	207	294	236	259
Cr	1	1	0.9	0.8	0.8	0.4	0.8	0.9
INR	0.98	1.1	1.05		1.06	1.05		1.13

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 3								
GCS	6T	8T	11T	15	15	15	15	15
Pao2/FiO2	302	449	443	98 sat	98 sat	98 sat	97 sat	
AST	216			31	23	20		
ALT	100			33	26	26		
WBC	14.2	9.9	8.6	6.8	5.6	6.9	9.7	
HgB	13.5	11.7	10.5	11.5	10.4	11	11.7	
Platelets	219	165	162	159	180	222	273	
Cr	0.9	0.6	0.6	0.7	0.6	0.6	0.7	
INR	0.97			0.95	0.98	0.95		

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 6								
GCS	7T	7T	7T	8T	8T	8T	6T	8T
Pao2/FiO2	350	363	253	338	228	313	188[1]	302
AST	257	88	144	98	97	60	59	123
ALT	92	252	79	70	98	74	64	98
WBC	11.2	11.7	9.6	6.8	14.6	17.9	14.2	8.8
HgB	14.7	13.2	12.2	10.7	11.4	11.6	11.3	11.4
Platelets	223	186	178	194	195	247	298	342
Cr	1.2	1	0.9	0.9	0.7	0.7	0.5	0.6
INR	1.16	1.19	1.2	1.13	1.16	1.15	1.11	1.11

Figure 4 continued – Subjects 1-12 Safety Data, Baseline through Day 7

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 7								
GCS	7T	10T	15	15	15	15		
Pao2/FiO2	512	463	98 sat	98 sat	100 sat	100 sat		
AST	101	102	174	100				
ALT	39	36	40	38				
WBC	24.6	12.1	14.5	8.5				
HgB	15.1	11.2	10.8	10.9				
Platelets	223	127	131	153				
Cr	0.9	1	0.8	0.7				
INR	1.23	1.15	1.06	1.02				

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 10								
GCS	7T	7T	7T	3T	3T	6T	7T	6T
Pao2/FiO2	205	410	622	170[3]	ECMO	ECMO	ECMO	ECMO
AST	280	246	123	96		65	38	59
ALT	166	154	90	74		52	54	50
WBC	18	9.9	6.3	6.3	7.2	14.2	14.1	17.6
HgB	15.9	12.3	8.9	8.3	10.8	11	10.9	10.6
Platelets	293	146	153	183	156	151	167	157
Cr	1.3	0.8	0.8	0.7	0.9	0.9	0.6	0.6
INR	1.29	1.33	1.2	1.13	1.28	1.42	1.12	1.09

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 8								
GCS	7T	10T	10T	15	15	15	15	15
Pao2/FiO2	578	464	352	98 sat	100 sat	100 sat	100 sat	98 sat
AST	18	27	31	29				18
ALT	14	14	14	16				28
WBC	11.6	15.3	12.6	7	9.2	8.5	7.3	7.2
HgB	10.5	8.1	7.7	7.4	8.2	9.6	8.8	8.3
Platelets	183	155	152	143	330	267	299	312
Cr	0.7	0.7	0.6	0.6	0.1	0.6	0.6	0.8
INR	1.15	1.43	1.21	1.1	1.06			1.12

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 11								
GCS	7T	7T	7T	9T	7T	8T	10T	10T
Pao2/FiO2	480	272	210	340	98 sat	98 sat	96 sat	97 sat
AST	83	50	44	40	33	155	77	85
ALT	85	55	43	34	34	51	88	113
WBC	12.3	10.2	10	11.3	10.5	8.8	11.2	13.6
HgB	14	11.9	10.9	9.6	8.4	9.2	9.7	9.5
Platelets	325	197	146	173	195	250	306	367
Cr	1.2	0.9	0.9	0.8	0.8	1	0.9	1
INR	1.04	1.15		1.18	1.09	1.12	1.03	0.98

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 9								
GCS	8T	8T	8T	9T	7T	9T	8T	8T
Pao2/FiO2	415	245	100 sat	167[2]	100 sat	100 sat	100 sat	100 Sat
AST	132	66	54	30	21	28	64	40
ALT	128	77	66	50	40	48	82	84
WBC	21	12.3	12.5	11.5	9.7	11.6	12.9	14.8
HgB	16.21	10	8.6	8.7	8.6	9	8.9	8.2
Platelets	193	115	104	127	169	202	220	221
Cr	1.1	1	0.9	0.8	0.7	0.8	0.8	0.8
INR	1.26	1.48	1.29	1.15	1.02	1.03	1.1	1.1

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT 12								
GCS	7T	8T	8T	8T	11T	8T	6	8
Pao2/FiO2	750	348	100 sat	100 sat	100 sat	398	98 sat	99 sat
AST	122	93	62			23	41	51
ALT	84	80	63			38	62	64
WBC	11.9	11.1	9		10.9	10.1	12	11.9
HgB	15.2	8.8	8.3		9.1	8.6	9.1	9.8
Platelets	256	176	185		317	371	409	545
Cr	0.8	0.7	0.5		0.7	0.5	0.6	0.4
INR	1.22	1.23	1.05		1.05		1.04	1.01

Explanation of Abnormal P:F ratios in Figure:

[1] Subject 6, Day 6 – the subject underwent tracheostomy placement on the prior day. Review of the medical records show that after tracheostomy the subject's vent settings were changed to FiO2 of 80%. The subject was maintained on elevated FiO2 until the next day when an ABG was done with the resulting P:F ratio. It is likely that the subject either aspirated or derecruited alveoli during the procedure. This on top of an already present pneumonia is likely the cause for the low P:F. Chest X-ray showed no diffuse opacification concerning for ARDS/ALI.

[2] Subject 9, Day 3 – Thought not explicitly documented, it appears that respiratory therapy was adjusting vent settings in attempt to wean to CPAP. During these trials an ABG was run resulting in this low P:F ratio. Shortly after this value was obtained this subject was converted from SIMV to CPAP without complication, which leads us to believe that this P:F value was aberrant based on wean protocol/vent settings. The chest X-ray for this day and the next did show pathology specifically pleural effusion and atelectasis, but no diffuse opacities consistent with ARDS/ALI.

[3] Subject 10, Day 3 – On this day the subject was started on Dobhoff tube feedings. Approximately 2-3 hours post feed, the subject began having desaturations and difficulty oxygenating. Bronchoscopy was performed and the subject was found to have most likely aspiration of tube feeds. The subject's vent settings were adjusted to no avail. The subject was subsequently placed on ECMO for what appears to be severe aspiration pneumonitis. This particular event was submitted to the DSMB, IRB and HRPO.

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Figure 5 – Subjects 1-12, Safety Data, Baseline through Day 7

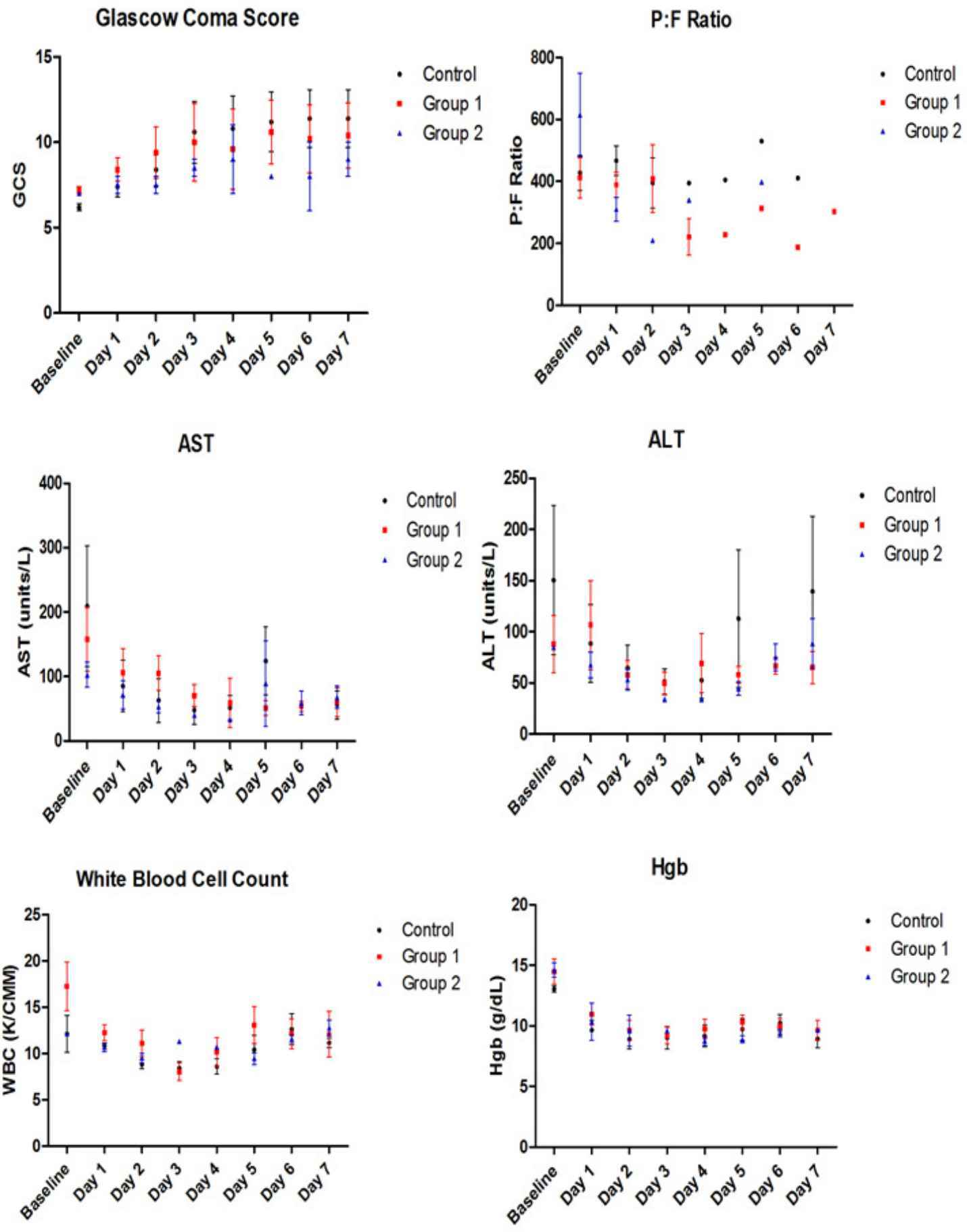

Figure 5 continued – Subjects 1-12, Safety Data, Baseline through Day 7

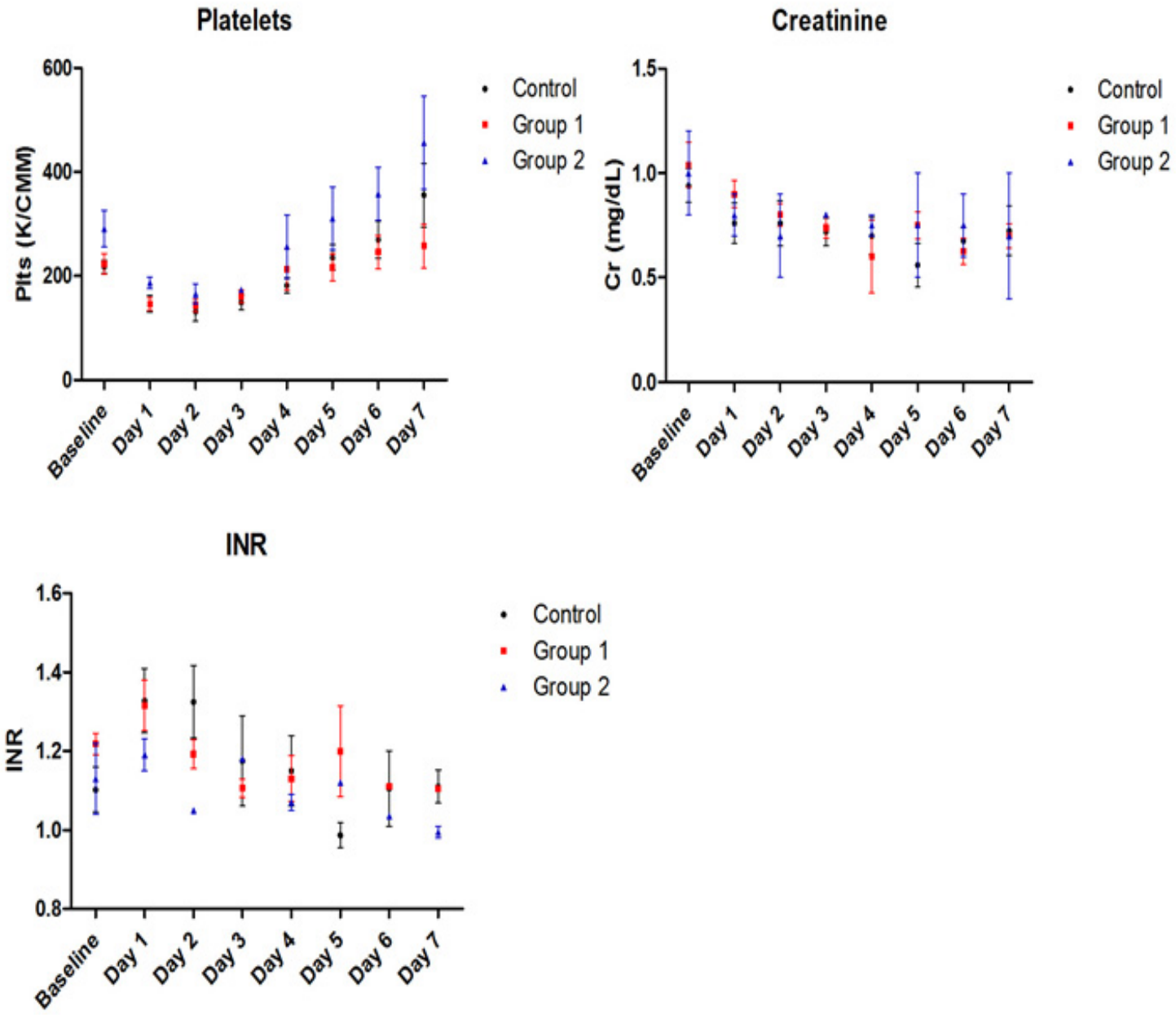

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Figure 6 – Subjects 1-12, Safety Data, Baseline through 6 Month Follow-Up

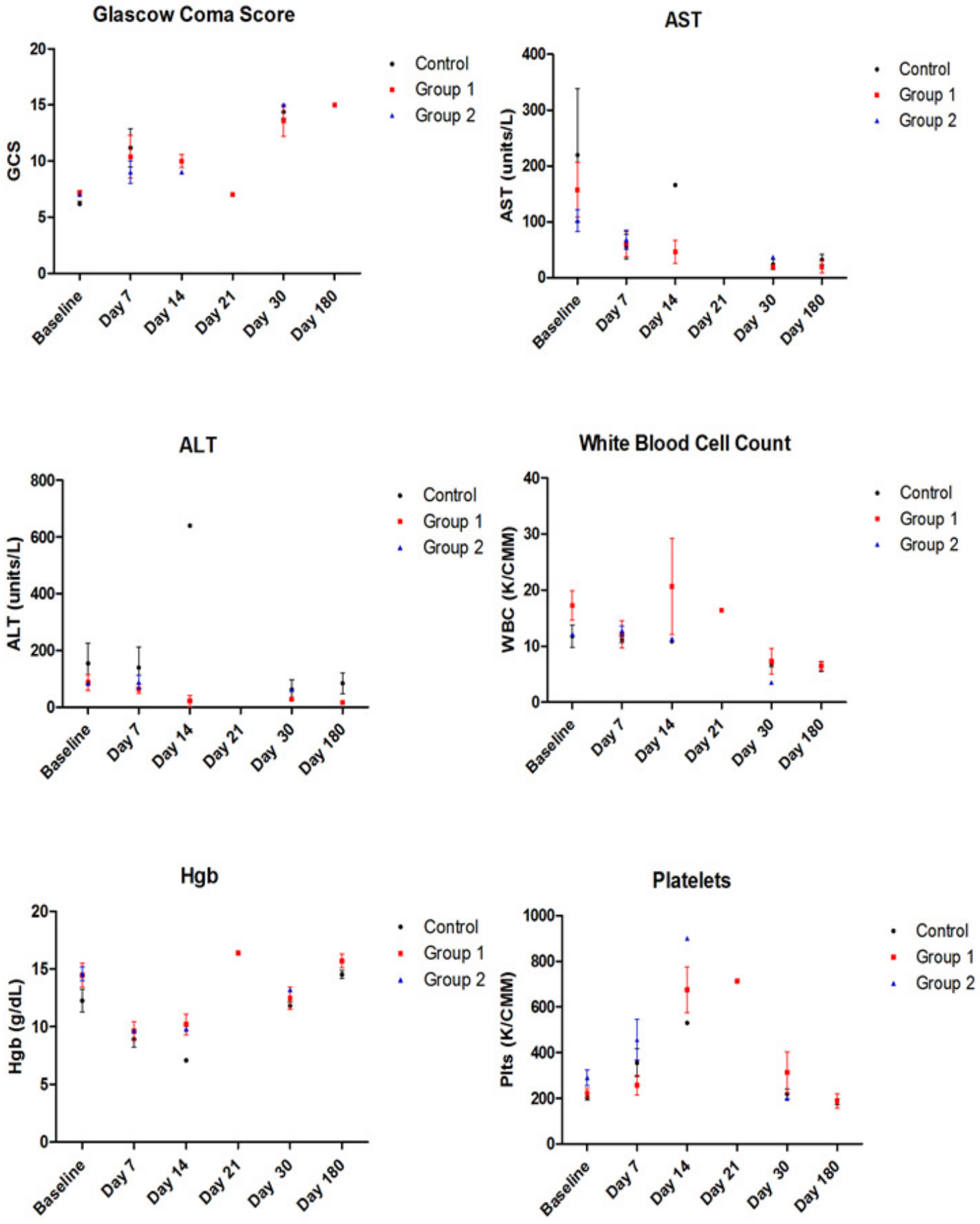
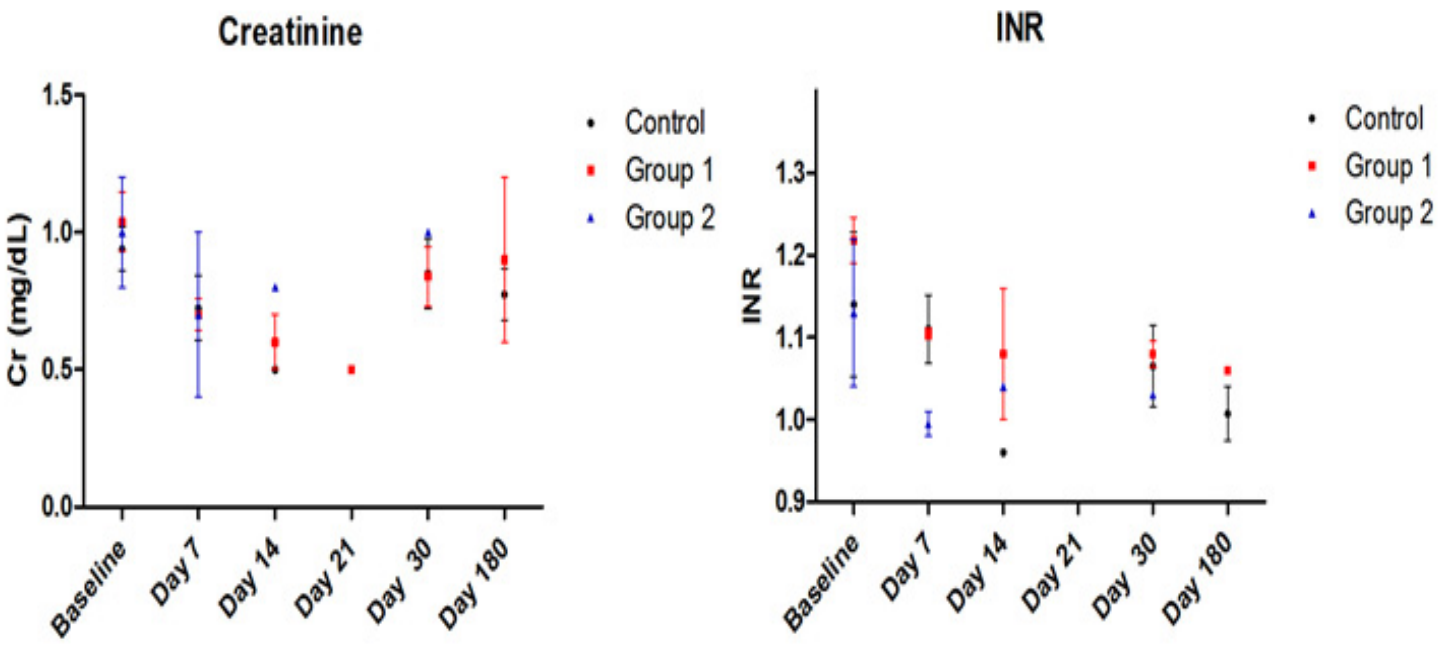


Figure 6 continued – Subjects 1-12, Safety Data, Baseline through 6 Month Follow-Up



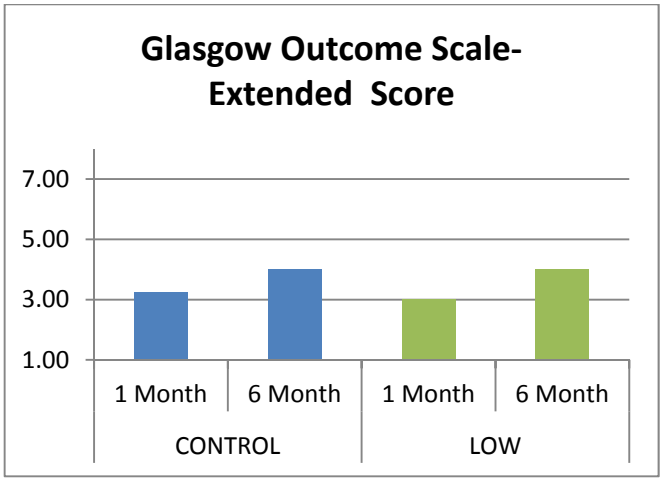
Secondary Outcomes

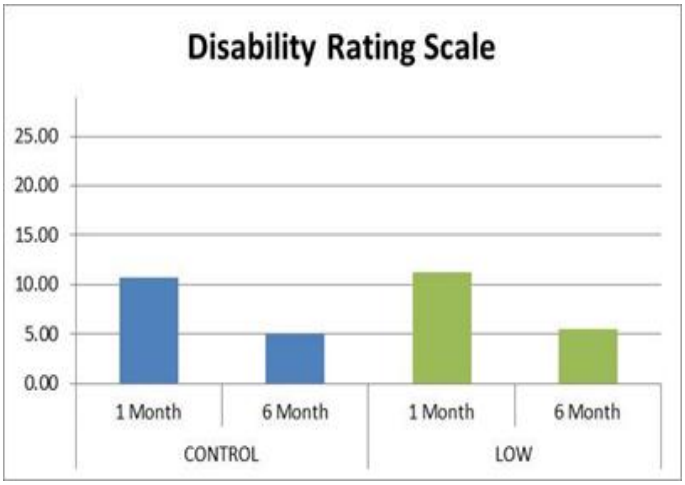
2. Functional outcomes measures

Neurobehavioral Outcomes

Neurobehavioral outcome data has been obtained on 10 of the 11 patients for the 1 month evaluation; one patient refused to complete the assessment. Six patients have completed the 6 month follow-up. Caregivers were interviewed regarding patients' level of global functioning. Figures 7-8 show global outcome scores by group and time of assessment. Glasgow Outcome Scale-Extended scores indicated functioning in the lower severe disability range in 7 of 9 patients at 1 month after injury and in 3 of 6 at follow-up. Mayo-Portland Adaptability Inventory-IV ratings examined overall disability as well as specific outcomes in Ability (sensory, cognitive, motor), Adjustment (behavior and psychological health) and Participation (social/community/ vocational) domains.

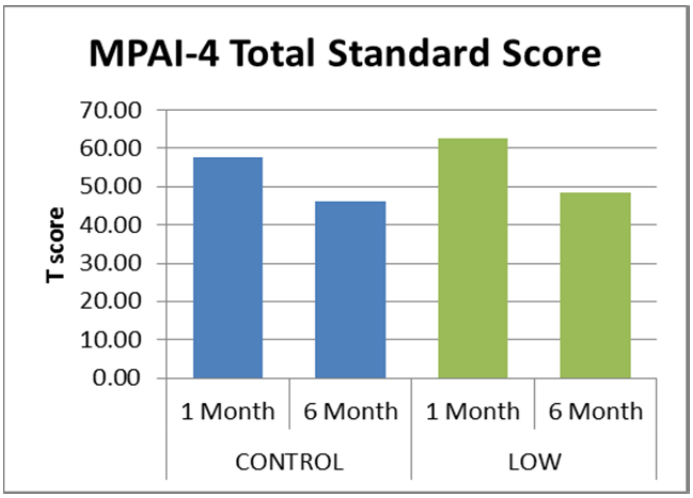
Figures 7 & 8

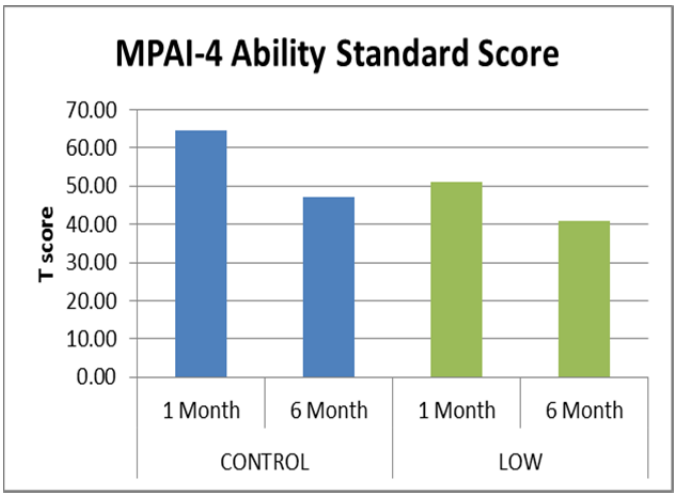




Figures 7 & 8 Initial scores for control (n=4) and low dose (n=5) groups on global measures of outcome suggested functioning in the moderate to severe disability range. 6m follow-up scores suggested similar improvement across time, indicated by increased GOS-E scores and decreased DRS scores in control (n=4) and low dose (n=2) groups.

Figures 9 & 10





Figures 9 & 10 Longitudinal scores on the Mayo-Portland Participation Index-IV (n=4 control & 2 low dose patients) show change over time in total scores. At follow-up, total scores were slightly better (lower) in the control group (*d*=-.33). The Ability score reflecting sensory, motor, and cognitive functioning tended to be more favorable in the low dose group (*d*=.58) while the Adjustment score reflecting mood, behavior, and social integration was more favorable in the control group (*d*=-2.11)

Neuropsychological testing was completed through direct evaluation. Scores were windsorized and assigned at 3.5 SDs below the mean when patients were cognitively or physically unable to complete a task. At the 1 month evaluation, scores were windsorized for 2 to 6 patients for each test. Figures 11 & 12 show more favorable delayed recall on a verbal declarative memory task in the low dose group and more favorable working memory scores in the control group. Accrual of follow-up data during the next budget year will allow evaluation of change from 1 to 6 months after injury in a larger sample.

Figures 11 &12

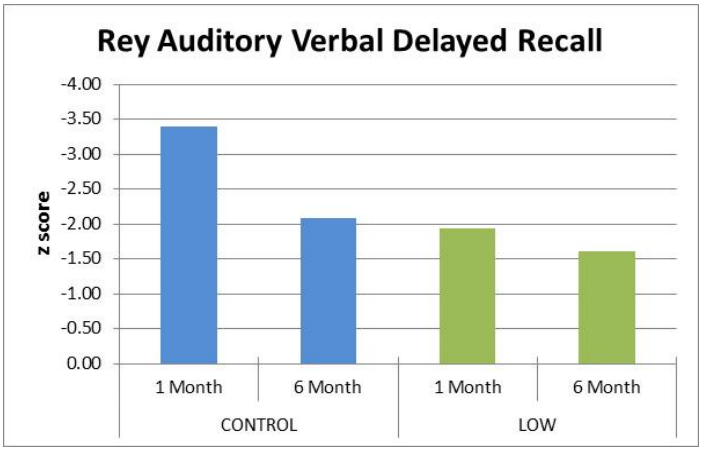


Figure 11 Verbal memory scores were more favorable (higher z score) in the low dose than in the no treatment group at both intervals.

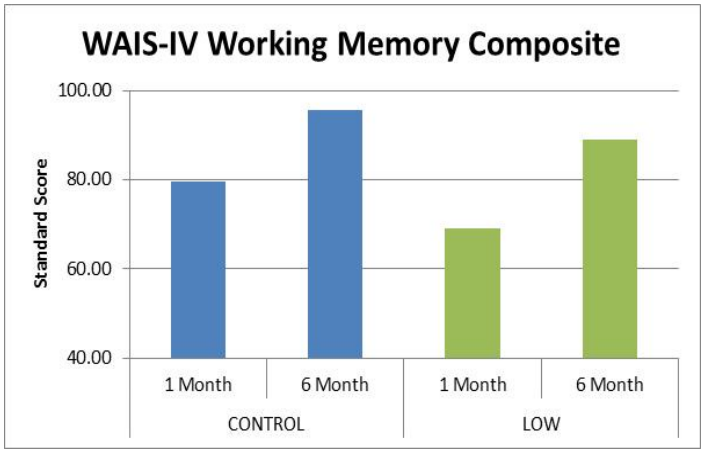


Figure 12 Verbal working memory standard scores were more favorable in the control than in the low dose group.

3. BMMNC infusion will reduce BBB permeability: Cytokines and Pro/Anti-Inflammatory Marker Evaluation

Inflammatory Marker analyses have not been performed to date.

4. BMMNC is neuroprotective and preserves grey matter and white matter volumes after TBI

A total of 12 adult patients have been enrolled and have completed their first neuroimaging session at their respective 1 month timepoint post-TBI. Of these 12 patients, a total of 6 have completed their 6 month follow-up MRI session. Four out of the first 5 subjects have completed both MRI sessions (e.g. subjects 001,003,004,005); two out of the next 7 subjects have completed both MRI sessions (e.g. subjects 006, 007). Thus far, only 1 subject has been lost for follow-up (e.g. subject 002). The remaining subjects (n=5) are in the queue for scheduling their 6 month follow-up MRI session. All data acquisitions were supervised by the imaging specialist (JJ); MRI sequences were repeated as necessary to acquire high quality data, all of which have been included in analyses (e.g. no datasets have been dropped due to poor image quality).

DTI Analyses

Following eddy current correction and motion correction (e.g. FSL), maps of fractional anisotropy (FA) and Mean Diffusivity (MD) were generated using TrackVis to obtain whole brain values of FA and MD as well as a focused analysis of the corpus callosum (CC). As shown in Figure 13, initial 1mo FA values for the whole brain varied across subjects, ranging from 0.31 to 0.43. At the 6mo follow-up MRI, whole brain FA values ranged across subjects from 0.30 to 0.39. Within subject change in whole brain FA values from 1mo to 6mo MRI sessions ranged from 0 (subject 007) to 0.13 (subject 003).

Figure 13

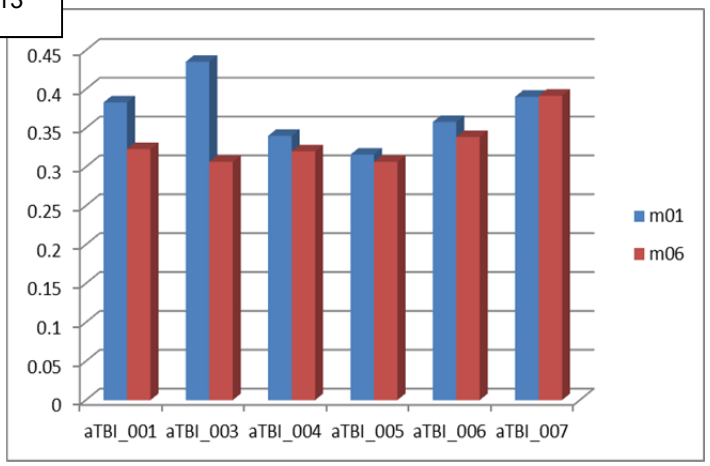
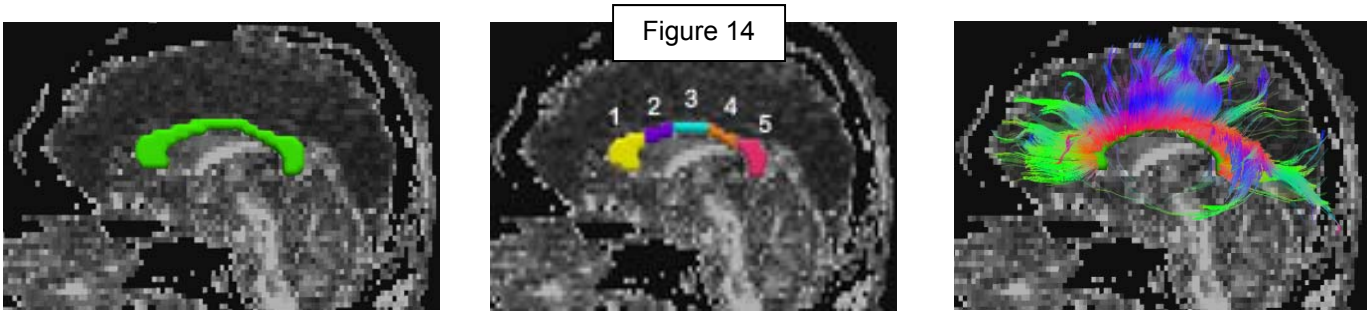


Figure 14



In addition to whole brain, targeted DTI analyses of the corpus callosum included FA and MD in the CC as a whole as well as a segmented CC parceled into 5 equidistant segments (see Figure 14).

As demonstrated in Figure 15, FA values in the CC as whole varied across subjects at both time points, 1mo and 6mo post-TBI. While most subjects had lower FA values at 6mo post-TBI (e.g. subjects 001, 003, 004, 005), two subjects had well-preserved FA values (e.g. subjects 006, 007).

Analyses of FA values across segments of the CC (Fig 16) yielded some spatial information as to which areas of the CC were exhibiting lowered FA values and which regions were less

Figure 15

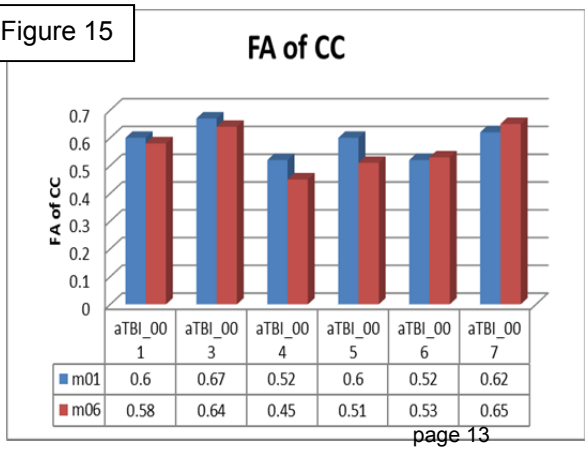
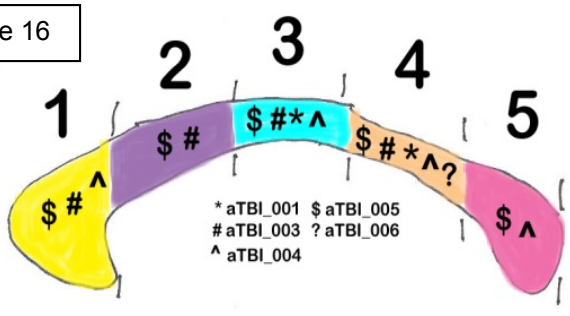


Figure 16



affected. Each subject's data for CC segments is presented separately in Figures 17 below.

Figures 17

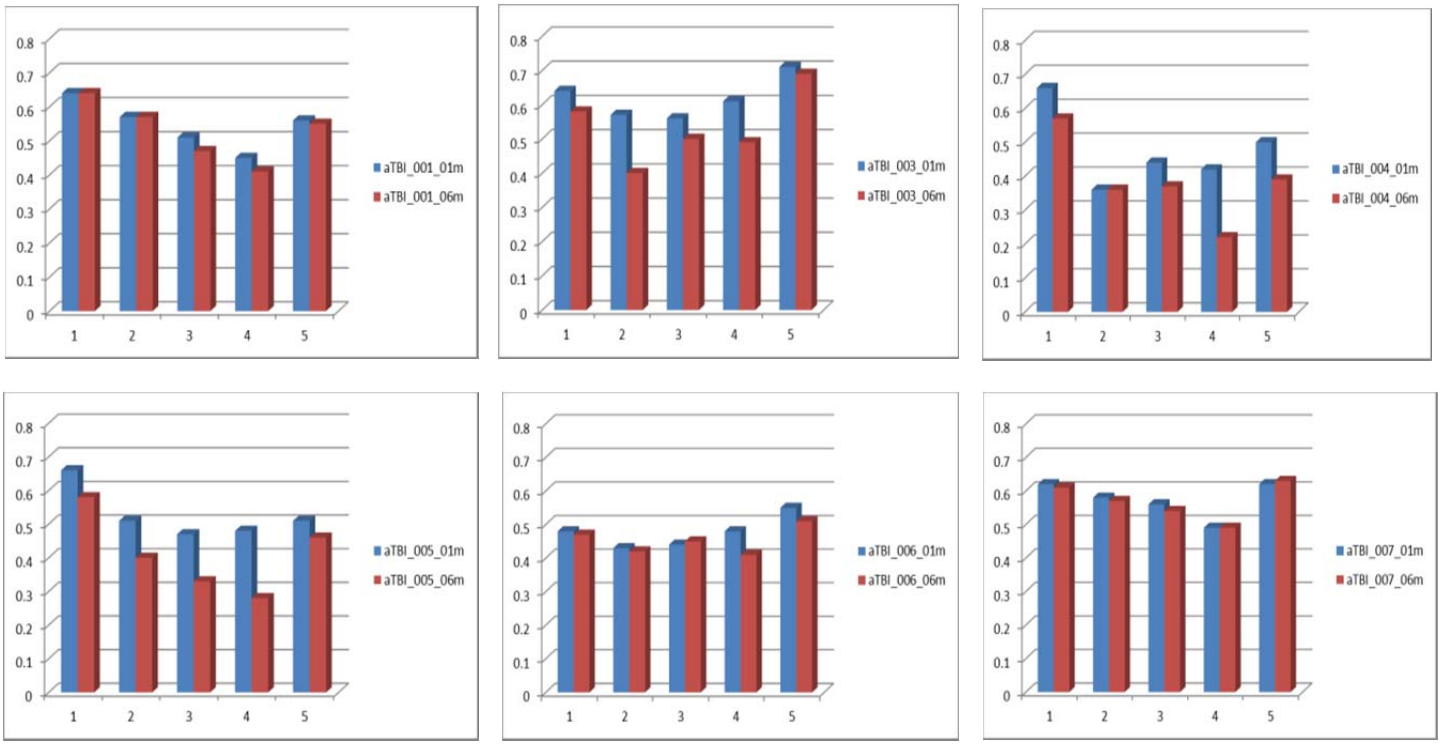
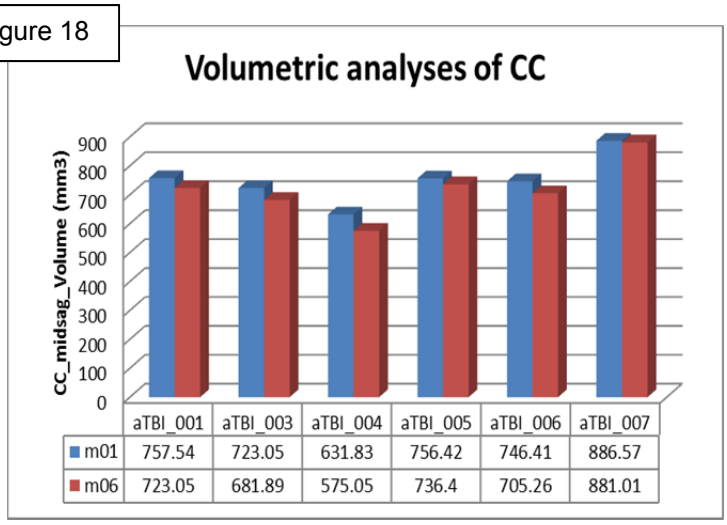


Figure 18



Volumetric Analyses

High-resolution T1-weighted images were used to conduct volumetric analyses of the CC. As shown in Figure 18, some volumetric loss between the 1mo and 6mo MRI is appreciated across all subjects, except for subject 007.

Key Research Accomplishments:

The FDA approved this protocol under IND 12620 on April 20, 2011.

Final approval from the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects was received on October 19, 2011.

Approval from the Army HRPO was received on December 20, 2011.

Recruitment was open on March 1, 2012.

Annual Report submitted June 1, 2012.

Current protocol Version 9 (3-1-13) approved by the IRB on April 8, 2013.

IRB continuing review approval was received on June 10, 2013.

To date, 12 subjects have been enrolled and have had plasma collected for neuroinflammatory markers during the acute period. All have returned for their 30-day follow-up MRI visit, and 6 have returned for their 6 month visit. One control subject is lost to follow-up at the 6 month visit.

Reportable Outcomes:

N/A

Conclusion:

N/A

References:

N/A

Appendices:

N/A

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